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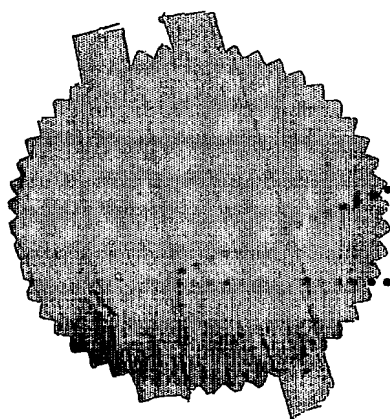
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Patent Office  
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Mumbai - 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy  
of Application and Provisional Specification filed on 21/08/2003 in respect of Patent  
Application No.837/MUM/2003 of SUN PHARMACEUTICAL INDUSTRIES LTD., ACME  
PLAZA, ANDHERI-KURLA ROAD, ANDHERI(E), MUMBAI - 400 059, INDIA, AN  
INDIAN COMPANY.

This certificate is issued under the powers vested in me under Section  
147(1) of the Patents Act, 1970.

.....  
Dated this 18<sup>th</sup> day of January 2005.



  
(R. BHATTACHARYA)

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Best Available Copy

**FORM 1**

**THE PATENTS ACT, 1970  
(39 OF 1970)**

**APPLICATION FOR GRANT OF A PATENT  
(See sections 5(2), 7, 54 and 135 and rule 33A)**

**We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA**

**AN INDIAN COMPANY**

hereby declare -

- (i) that we are in possession of an invention titled **"A PROCESS FOR PREPARATION OF BISPHOSPHONIC ACID COMPOUNDS"**
- (ii) that the provisional specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

**1) Mr. Patel Vijaykumar Muljibhai 2) Dr. Chitturi Trinadha Rao 3) Dr. Thennati Rajamannar;** of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

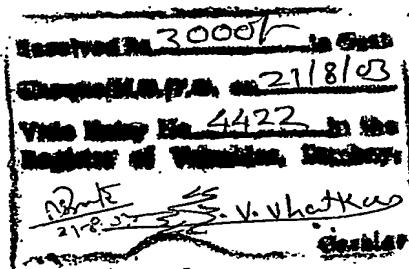
We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

**Dr. RATNESH SHRIVASTAVA,  
INTELLECTUAL PROPERTY CELL,  
SUN PHARMACEUTICAL INDUSTRIES LTD,  
ACME PLAZA, ANDHERI-KURLA ROAD,  
ANDHERI (E), MUMBAI-400 059, INDIA,  
TELEPHONE NO-28397632, FACSIMILE NO- 28212110.**

837/MUM/2003  
21/8/2003



FORM 2

THE PATENTS ACT, 1970  
(39 OF 1970)

PROVISIONAL SPECIFICATION  
(See section 10; rule 13)

**A PROCESS FOR PREPARATION OF BISPHOSPHONIC ACID COMPOUNDS**

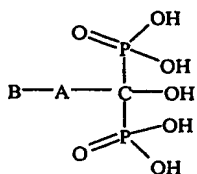
**SUN PHARMACEUTICAL INDUSTRIES LTD.**

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

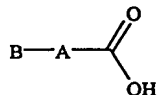
**The following specification describes the nature of this invention.**

## A PROCESS FOR PREPARATION OF BISPHOSPHONIC ACID COMPOUNDS

The present invention relates to an improved process for preparation of bisphosphonic acid compounds, represented by a compound of formula 1. More specifically the present invention relates to a process for preparation of compound of formula 1 by reaction of a compound of formula 2 with a mixture of phosphorous acid and  $\text{PCl}_3$  in sulfolane.

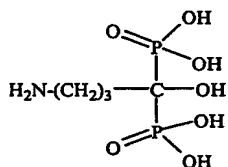


**Formula 1**

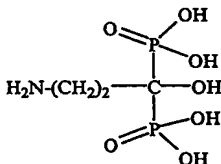


**Formula 2**

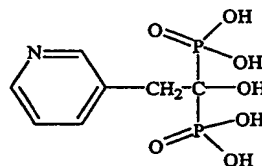
The present invention particularly relates to a process for the preparation of bisphosphonic acid compounds of formulae 3 to 10, namely, alendronic acid, pamidronic acid, risedronic acid, zoledronic acid, ibandronic acid, minodronic acid, neridronic acid and olpadronic acid, respectively.



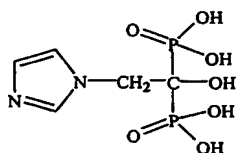
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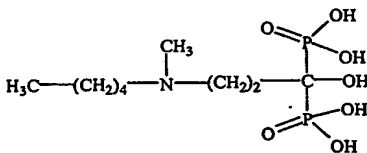
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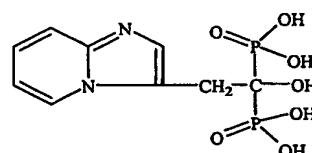
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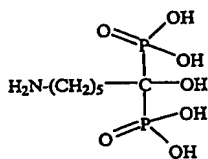
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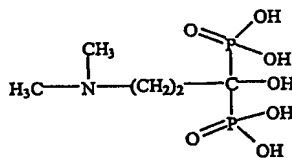
**Formula 7**



**Formula 8**



**Formula 9**



**Formula 10**

Bisphosphonate compounds have generally been prepared by the reaction of carbonyl compounds with phosphorous halides. 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid, a compound of formula 3) or salts thereof are prepared by the reaction of 4-aminobutyric acid with a mixture of phosphorous acid and one of the three phosphorous chlorides; viz. phosphorous trichloride ( $\text{PCl}_3$ ), phosphorous oxychloride ( $\text{POCl}_3$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ), then quenching the reaction mixture with water followed by heating to hydrolyze the phosphorous intermediates.

Different processes using a variety of different solvents/carriers have been reported in the literature for making the reaction mixture homogenous for preparation of bisphosphonates, however they have some disadvantages associated with their use.

United states patent No. 4407761 (referred to herein as the '761 patent, Indian reference not available) teaches preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid besides other phosphonic acids. However, high amounts of orange solid termed 'orange pyrophoric acid' containing phosphorous and oxidized phosphorous is generated, which is sticky, non-stirrable, difficult to handle and undesirable by-product. In the '761 patent chlorobenzene is used to attempt solubilization of the reaction mixture. The process is not suitable for industrial scale production. Solvent such as chlorobenzene is harmful, an irritant for skin, eyes and environmentally hazardous.

United States Patent No. 4705651 (Indian reference not available) teaches a similar procedure with different molar ratios, which is still not very attractive for industrial scale up.

United States Patent Nos. 4922007 and 5019651 teach the use of methanesulfonic acid for solubilizing the reaction components. Methanesulfonic acid is expensive, corrosive, light sensitive and irritant. The reaction between methanesulfonic acid and  $\text{PCl}_3$  is exothermic and can become uncontrollable. Also large quantity of alkali would be required in the work up for neutralization.

United States Patent No. 5908959 teaches use of long chain glycols to attempt to stop the solidification of reaction mixture, however it can not be totally avoided and these glycols can not be recycled as they get converted in to chloride derivatives.

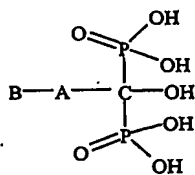
The PCT application WO 02/090367 teaches use of aralkyl or alkyl ethoxylates or triglycerides such as plant or animal oils for solubilization of the reaction mixture.

United States Patent Application No. 2003/0013918 teaches use of an amine hydrochloride in preparation of bisphosphonates from reaction of a carbonyl compound with a phosphorous halide. This process involves use of concentrated HCl acid as a reactant.

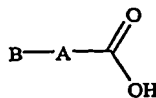
The present invention provides a process wherein a water miscible neutral solvent such as sulfolane is used for preparation of bisphosphonic acid compounds, making the process safe and convenient. We have also found that another water miscible neutral solvent such as 1,2-dimethoxyethane can also be used, however sulfolane was observed to provide better yield. The process of the present invention is suitable for industrial scale up and can be used commercially. Since sulfolane is water miscible and neutral, the reaction mixture can be quenched into water, the intermediates subsequently hydrolyzed and the final product directly isolated from reaction mixture.

The present invention provides a process for preparation of bisphosphonic acid, a compound of formula 1 or a salt thereof comprising,

- a) reacting a carboxylic acid compound of formula 2 with phosphorous acid and a phosphorous chloride selected from  $\text{PCl}_3$ ,  $\text{PCl}_5$  and  $\text{POCl}_3$ , in sulfolane;

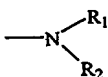


**Formula 1**



**Formula 2**

wherein A is a straight chain alkyl, a branched alkyl or a cyclic alkyl chain with up to 10 carbon atoms, which can be optionally interrupted by hetero atoms and B can be an aromatic or heteroaromatic radical which can be optionally substituted; or



wherein,  $R_1$  and  $R_2$  may be selected from hydrogen or straight chain or branched lower alkyl, and

b) recovering the compound of formula 1 or salt thereof.

The moiety A is a straight chain, a branched alkyl chain or a cyclic alkyl chain with up to 10 carbon atoms, which can be optionally interrupted by hetero atoms for e.g., oxygen and sulphur.

The aromatic or heteroaromatic radical mentioned as substituent for moiety B may be any aromatic or heteroaromatic radical, that may be monocyclic or polycyclic for example, phenyl, pyridinyl, imidazolyl, indolyl, imidazopyridinyl etc. that may be unsubstituted or substituted.

The substituents  $R_1$  and  $R_2$  both may be same or different and selected from hydrogen or straight chain or branched lower alkyl. The lower alkyl are containing up to 5 carbon atoms for e.g. methyl, ethyl, isopropyl radicals.

In the process of the present invention, the preferred phosphorous chloride used is phosphorous trichloride ( $\text{PCl}_3$ ).

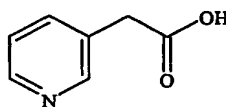
It has been found that bisphosphonic acids can be obtained in a safe manner, in high yield and purity when using the process of the invention. The present invention uses sulfolane which is relatively safe and inexpensive, water miscible neutral solvent for preparation of bisphosphonic acids. The hydrolysis of the formed phosphorous intermediates can be carried out in same reaction mixture, and if desired, the pH can be adjusted to about 4.3 and the sodium salt of the bisphosphonic acid can be directly obtained in pure form. It is observed that the process of the present invention provides compounds of formulae 4, 5 and 6 in improved yield.

The compound of formula 2 and the phosphorous acid in sulfolane are reacted with phosphorous trichloride at a suitable temperature, for example, between about 35°C to about 150°C, preferably at about 60 to about 70°C, at which temperature the phosphorylation reaction is completed in about 3 hours.

In one embodiment the present invention provides a process for preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, a compound of formula 3 or salt thereof by reacting 4-aminobutyric acid with phosphorous acid and  $\text{PCl}_3$  in sulfolane.

In second embodiment the present invention provides a process for preparation of 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, a compound of formula 4 or salt thereof by reacting 3-aminopropionic acid with phosphorous acid and  $\text{PCl}_3$  in sulfolane.

In third embodiment the present invention provides a process for preparation of risedronic acid or risedronate, a compound of formula 5 or salt thereof by reacting 3-pyridylacetic acid,

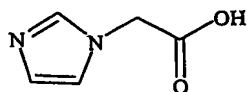


**Formula 11**

a compound of formula 11 with phosphorous acid and  $\text{PCl}_3$  in sulfolane.



In fourth embodiment the present invention provides a process for preparation of zoledronic acid or zoledronate, a compound of formula 6 or salt thereof by reacting 1-imidazolylacetic



**Formula 12**

acid, a compound of formula 12 with phosphorous acid and  $\text{PCl}_3$  in sulfolane.

## Examples

### Example 1

#### Preparation of alendronate sodium trihydrate

A suspension of 4-aminobutyric acid (25g, 0.242mol) and phosphorous acid (29.8g, 0.364mol) in sulfolane (90ml) was heated to 75° C for 30 min. The mixture was cooled to 35-40° C and then gradually introduced phosphorous trichloride (72ml, 0.824mol) while maintaining the temperature between 35-45° C. The mixture was heated to 63-67°C for 3 hours whereby a thick white mass resulted. It was then cooled to 0-5°C and quenched by slow addition of water (250ml) over a period of 1 hr. The resulting clear solution is heated at 100° C for 3 hrs, cooled to ambient temperature and charcoalized. To the charcoalized solution is added 45%w/w sodium hydroxide solution at 0-5° C until pH is 4.3. The mixture is then stirred for 3hrs at 0-5° C and the crystallized product is filtered, washed sequentially with chilled water (100ml), rectified spirit (75ml) and dried in air oven at 55-60° C until water content is between. 16-18% w/w. Yield 54g, (68.5%), Appearance: white crystalline solid, purity >99.0%.

### Example 2

#### Preparation of pamidronate (pamidronic acid)

A suspension of 3-aminopropionic acid (25g, 0.280mol) and phosphorous acid (34.5g, 0.421mol) in sulfolane (90ml) is heated to 75° C for 30 min. The mixture is cooled to 35-40° C and then gradually introduced phosphorous trichloride (83ml, 0.954mol) while maintaining the temperature between 35-45° C. The mixture is heated to 63-67° C for 3 hrs, whereby white solid results. It is then cooled to 0-5° C and quenched by slow addition of water (250ml) at 0-5° C over a period of 1 hr. The resulting clear is charcoalized and is heated at 100° C for 3 hrs, cooled to ambient temperature. Cooled the charcoalized solution and stirred for 4hrs at 0-5° C. The crystallized product is filtered, washed sequentially with chilled water (100ml), rectified spirit (75ml) and dried in air oven at 55-60° C until water content is less than 0.5% w/w. Yield 41.4g, (62.7%), Appearance : white crystalline solid, purity >99.0%.

### Example 3

#### Preparation of risedronate sodium trihydrate

A suspension of 3-pyridylacetic acid hydrochloride (25g, 0.144mol) and phosphorous acid (17.7g, 0.216mol) in sulfolane (90ml) is heated to 75° C for 30 min. The mixture is cooled to 35-40° C and then gradually introduced phosphorous trichloride (42.7ml, 0.49mol) while maintaining the temperature between 35-45° C. The mixture is heated to 63-67° C for 3 hours whereby a thick white mass results. It is then cooled to 0-5° C and quenched by slow addition of water (250ml) at 0-5° C over a period of 1 hr. The resulting clear solution is charcoalized, the charcoalized solution is heated at 100° C for 3 hrs, cooled to ambient temperature and is added 45%w/w sodium hydroxide solution at 0-5° C until pH is 4.3. The mixture is then stirred for 3hrs at 0-5° C and the crystallized product is filtered, washed sequentially with chilled water (100ml), rectified spirit (75ml) and dried in air oven at 55-60° C until water content is between. 16-18% w/w. Yield 41g, (76%), Appearance: white crystalline solid, purity >99.0%.

### Example 4

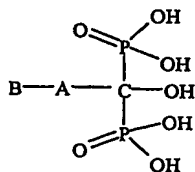
#### Preparation of zoledronic acid monohydrate

A suspension of 1-imidazolyl acetic acid (50g, 0.396mol) and phosphorous acid (48.7g, 0.594mol) in sulfolane (180ml) is heated to 75° C for 30 min. The mixture is cooled to 35-40° C and then gradually introduced phosphorous trichloride (117ml, 1.346mol) while maintaining the temperature between 35-45° C. The mixture is heated to 63-67° C for 3 hrs, whereby white solid results. It is then cooled to 0-5° C and quenched by slow addition of water (500ml) at 0-5° C over a period of 1 hr. The resulting clear solution is heated at 100° C for 3 hrs, cooled to ambient temperature and charcoalized. To the charcoalized solution is added acetone(800ml). The mixture is then stirred for 4hrs at 20-25° C and the crystallized product is filtered, washed sequentially with chilled water (200ml), acetone (100ml) and dried in air oven at 55-60° C until water content is between. 6.2-7.2% w/w. Yield 81.3g, (70.7%), Appearance: white crystalline solid.

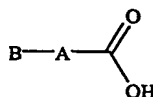
The present invention is further defined by the following:

A] A process for preparation of bisphosphonic acid, a compound of formula 1 or a salt thereof comprising,

- a) reacting a carboxylic acid compound of formula 2 with phosphorous acid and a phosphorous chloride selected from  $\text{PCl}_3$ ,  $\text{PCl}_5$  and  $\text{POCl}_3$ , in sulfolane

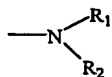


**Formula 1**



**Formula 2**

wherein A is a straight chain alkyl, a branched alkyl or a cyclic alkyl chain with up to 10 carbon atoms, which can be optionally interrupted by hetero atoms and B can be an aromatic or heteroaromatic radical which can be optionally substituted; or



wherein,  $\text{R}_1$  and  $\text{R}_2$  may be selected from hydrogen or straight chain or branched lower alkyl, and

- b) recovering the compound of formula 1 or salt thereof.

B] A process for preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, a compound of formula 3, or a salt thereof comprising,

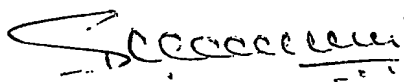
- a) reacting 4-aminobutyric acid with phosphorous acid and  $\text{PCl}_3$  in sulfolane; and  
b) recovering compound of formula 3 or a salt thereof.

C] A process for preparation of 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, a compound of formula 4, or a salt thereof comprising,

- a) reacting 3-aminopropionic acid with phosphorous acid and  $\text{PCl}_3$  in sulfolane; and  
b) recovering compound of formula 4 or a salt thereof.

- D] A process for preparation of compound of formula 5, or a salt thereof comprising,
- a) reacting a compound of formula 11 with phosphorous acid and  $\text{PCl}_3$  in sulfolane;
  - and,
  - b) recovering compound of formula 5 or a salt thereof.
- E] A process for preparation of compound of formula 6, or a salt thereof comprising,
- a) reacting a compound of formula 12 with phosphorous acid and  $\text{PCl}_3$  in sulfolane;
  - and,
  - b) recovering compound of formula 6 or a salt thereof.

Dated this 20<sup>th</sup> day of August 2003.



**DILIP SHANGHVI**  
**CHAIRMAN AND MANAGING DIRECTOR**  
**SUN PHARMACEUTICAL INDUSTRIES LIMITED**

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